This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Broflanilide

(Pesticides)

Food Safety Commission of Japan (FSCJ)
October 2019

ABSTRACT

FSCJconducted the risk assessment of an insecticide, Broflanilide (CAS No. 1207727-04-5), based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice and soybean), residues in plants, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction activity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity (rats) and MoAs of tumorigenesis in the testis, uterus and ovaries in rats.

Plasma concentration of broflanilide and metabolite B were measured in 90-day subacute toxicity studies in rats, a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice.
Since the plasma concentration of broflanilide and metabolite B showed non-linear temporal changes in these studies, their absorption in these studies as well as in kinetic studies seemed to be saturated.
In addition, the plasma concentration of metabolite B was consistently higher than that of broflanilide suggesting that broflanilide was rapidly metabolized into metabolite B in the body. There was no sex difference of the changes in the plasma concentration in these studies except 90-day subacute toxicity studies.
Major adverse effects of broflanilide observed are suppressed body weight, effects on blood such as anemia (rats), increased organ weight in the adrenal gland, vacuolation of the adrenal cortex and stromal cell in the ovary (rats), increased organ weight in the ovary, and uterine glandular hyperplasia (rats).
Broflanilide showed none of neurotoxicity, effects on reproductive activity, teratogenicity, genotoxicity and immunotoxicity.

In a two-year combined chronic toxicity/carcinogenicity study in rats, total incidence of testicular interstitial cell tumors in male rats (at hithest dose), endometrial adenocarcinoma of uterus (at 2 hiehst doses) and stromal cell tumors of gonadal cords (luteomas, ovarian theca cell tumors, granulosa cell tumors, and gonadal cord mesenchymal tumors) (at 2 hiehest doses) was increased. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and it was considered possible to establish a threshold dose in the assessment.

From the above results, broflanilide (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed adverse effect level (NOAEL) in all tests was 1.7 mg/kg bw/day in a chronic toxicity group of the two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.017 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

Since no toxicological effects that would likely be elicited by a single dose of broflanilide was observed, FSCJ considered it was unnecessary to specify the ARfD.

Table 1. *Levels relevant to toxicological evaluation of broflanilide*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rats	90-day subacute toxicity study	0, 500, 1 500, 5 000, 15 000 ppm M: 0, 35, 104, 345, 1 110 F: 0, 41, 126, 418, 1 240	M: - F: -	M: 35 F: 41	M/F: Vacuolation in the adrenal cortical cells (zone fasciculate and zona glomerulosa)
	90-day subacute neurotoxicity study	0, 1 500, 5 000, 15 000 ppm M: 0, 99, 320, 1040 F: 0, 118, 423, 1 140	M: 1 040 F: 1 140	M: - F: -	M/F: No toxicity was observed. (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study	Chronic toxicity group: 0, 30, 100, 300, 1 500, 15 000 ppm Carcinogenicity group: 0, 100, 300, 1 500, 15 000 ppm Chronic toxicity group: M: 0, 1.7, 5.7, 16, 84, 822 F: 0, 2.1, 7.2, 20, 104, 1 130 Carcinogenicity group: M: 0, 4.5, 14, 70, 709 F: 0, 5.9, 19, 95, 953	M: 1.7 F: - (Carcinogenicity group): M: 14.5 F: - (Chronic toxicity group) M: 1.7 F: 7.2	M: 5.7 F: 5.9 (Carcinogenicity group): M: 14 F: 5.9 (Chronic toxicity group) M: 5.7 F: 20	M: Vacuolation in the adrenal cortical cells (all zone). F: Vacuolation in the ovarian stromal cells. (M: testicular interstitial cell tumors. F: Total incidence of stromal cell tumors derived from gonadal stroma and endometrial adenocarcinoma of uterus.)
	Two-generation reproductive activity study	0, 30, 100, 300, 1 500, 15 000 ppm PM : 0, 2.3, 7.5, 22.6, 112, 1 150 PF : 0, 2.5, 8.6, 25.6, 128, 1 290 F_1M : 0, 2.6, 8.6, 25.6, 128, 1 290 F_1F : 0, 2.7, 9.1, 28.7, 137, 1 390	Parent PM: 2.3 PF: 2.5 F_1M: 2.6 F_1F: 2.7 Offspring PM: 22.6 PF: 26.7 F_1M: 25.6 F_1F: 28.7	Parent PM: 7.5 PF: 8.3 F_1M: 8.6 F_1F: 9.1 Offspring PM: 112 PF: 126 F_1M: 128 F_1F: 137	Parent: M/F: Vacuolation of the adrenal cortical cells (zone fasciculate and zona glomerulosa) Offspring: Suppressed body weight (No effect on reproductive activity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Developmental toxicity study	0, 100, 300, 1 000	Dams: 1 000 Fetuses: 1 000	Dams: - Fetuses: -	Dams and fetuses: No toxicity was observed. (No teratogenicity)
Mice	90-day sub-acute toxicity study	0, 200, 1 500, 7 000 --- M: 0, 26.3, 199, 955 F: 0, 32.3, 230, 1 150	M: 955 F: 230	M: - F: 1 150	M: No toxicity was observed. F: Vacuolation of the adrenal cortical cells (zone fasciculate)
	78-week carcinogenicity study	0, 200, 1 500, 7 000 ppm --- M: 0, 21, 157, 745 F: 0, 22, 172, 820	M: 745 F: 172	M: - F: 820	M: No toxicity was observed. F: Increase in absolute and relative weight of the adrenal gland. (No carcinogenicity)
Rabbits	Developmental toxicity study	0, 100, 300, 1 000	Dams: 1 000 Fetuses:1 000	Dams: - Fetuses: -	Dams and Fetuses: No toxicity was observed (No teratogenicity)
Dogs	90-day subacute toxicity study	0, 100, 300, 1 000	M: 300 F: 300	M: 1 000 F: 1 000	M/F: Increase in absolute and relative weight of the liver.
	One-year chronic toxicity study	0, 100, 300, 1 000	M: - F: 100	M: 100 F: 300	M: Adrenal cortical cell hypertrophy (zona fasciculate, diffuse). F: Increase in absolute and relative weight of the adrenal gland.
ADI			NOAEL: 1.7 SF: 100 ADI: 0.017		
The critical study for setting ADI			Chronic toxicity group of Two-year combined chronic toxicity/carcinogenicity study in rats.		

ADI: Acceptable Daily Intake, NOAEL: No-observed-adverse-effect level, SF: Safety factor
-: NOAEL or LOAEL could not be specified.
[1)]The adverse effect observed at LOAEL